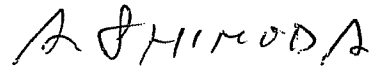


Statement of True Translation

I, SHIMODA Akira, translator to the Tokyo IP Firm. Kyobashi-Nichiei Bldg. 4F, Kyobashi 3-chome 34, Chuo-ku, Tokyo, Japan, hereby declare that I am conversant with the English and Japanese languages and am a competent translator thereof. I declare further that to the best of my knowledge and belief the following is a true and correct translation of Japanese Patent Application No. JP2004-023338.

November 12, 2010

A handwritten signature in cursive script, appearing to read 'A. Shimoda', is written above a horizontal line.

SHIMODA Akira

## Method For Producing Asymmetric Hydroxymethylated Compounds

### Field of the Invention

[0001]

The present invention relates to an asymmetric hydroxymethylation reaction and more particularly to a production method for an asymmetric hydroxymethylated compound and an catalyst thereof.

### Prior Art

[0002]

The reaction between a silicon enolate and formaldehyde under the presence of a Lewis acid is a useful method to synthesize  $\alpha$ -hydroxymethyl carbonyl compounds. However, a catalytic asymmetric reaction is extremely difficult to achieve, and examples with high selectivity have not been reported (References 1 to 2).

[0003]

Reference 1:

Manabe, K.; Ishikawa, S.; Hamada, T.; Kobayashi, S. Tetrahedron 2003, 59, 10439.

Reference 2:

Ozasa, N.; Wadamoto, M.; Ishihara, K.; Yamamoto, H. Synlett 2003, 2219.

Reference 3:

Bolm, C.; Ewald, M.; Felder, M.; Schlingloff, G. Chem. Ber. 1992, 125, 1169.

### Problems to be solved by the Invention

[0004]

The present invention presents a catalyst that allows an asymmetric hydroxymethylation reaction to proceed with excellent asymmetric selectivity and a production method for asymmetric hydroxymethylated compounds using the catalyst.

### Means to solve the Problems

[0005]

The inventors discovered that a catalytic asymmetrical hydroxymethylation reaction proceeded with excellent asymmetric selectivity when a combination of chiral ligands (see Reference 3) and a scandium triflate was used. The present invention was completed based on the discovery. A commercially available aqueous formaldehyde solution (formalin) can be used directly to the reaction.

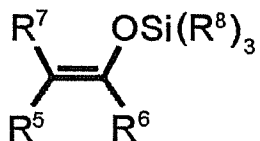
The catalytic system of the present invention is not only useful in the synthesis of asymmetric materials but also can provide an important direction for the development of catalytic asymmetric reactions in aqueous media.

[0006]

That is, the present invention is a method for producing an asymmetric hydroxymethylated compound, comprising reacting a silicon enolate and formaldehyde, in the presence of a catalyst, in an aqueous solution or a mixed solvent of water and an

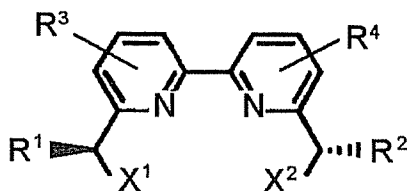
organic solvent,

wherein the silicon enolate is represented by the following formula (chemical formula 2):



wherein R<sup>5</sup> to R<sup>7</sup> are hydrogen atoms, aliphatic hydrocarbon groups, monocyclic or polycyclic alicyclic hydrocarbon groups, monocyclic or polycyclic aromatic or aliphatic hydrocarbon groups or heterocyclic groups and R<sup>8</sup>, may be identical or different, are hydrocarbon groups, and

the catalyst is obtained by mixing a ligand or its symmetric isomer and a Lewis acid, wherein the ligand is represented by the following formula (chemical formula 1):



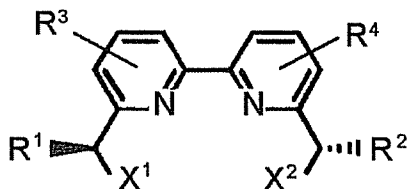
wherein R<sup>1</sup> and R<sup>2</sup>, may be identical or different, are hydrogen atoms, alkyl groups or aryl groups, at least one of R<sup>1</sup> and R<sup>2</sup> contains at least three carbon atoms, R<sup>3</sup> and R<sup>4</sup>, may be identical or different, are hydrogen atoms, alkyl groups containing one to four carbon atoms or alkoxy groups, X<sup>1</sup> and X<sup>2</sup>, may be identical or different, are represented by -OH, -SH or -NHR<sup>9</sup>, wherein R<sup>9</sup> is a hydrogen atom or an alkyl group, and

the Lewis acid is represented by MY<sub>n</sub>, wherein M is Cu, Zn, Fe, Sc or a lanthanoid element, Y is a halogen atom, OAc, OCOCF<sub>3</sub>, ClO<sub>4</sub>, SbF<sub>6</sub>, PF<sub>6</sub> or OSO<sub>2</sub>CF<sub>3</sub> and n is 2 or 3.

#### Detailed Description of the Invention

[0007]

The catalyst used in the present invention is obtained by mixing a ligand having the following structure (chemical formula 1):



and a Lewis acid represented by MY<sub>n</sub>.

[0008]

R<sup>1</sup> and R<sup>2</sup> represent hydrogen atoms, alkyl groups or aryl groups, preferably alkyl groups or aryl groups. They may be identical or different, preferably identical. At least one of R<sup>1</sup> and R<sup>2</sup> needs to be bulky and, more specifically, needs to contain at least three carbon atoms.

$R^3$  and  $R^4$  represent hydrogen atoms or alkyl or alkoxy groups having one to four carbon atoms but are preferably hydrogen atoms. . They may be identical or different, preferably identical.

[0009]

$X^1$  and  $X^2$  represent  $-OH$ ,  $-SH$  or  $-NHR^9$ , preferably  $-OH$ , where  $R^9$  represents a hydrogen atom or an alkyl group, preferably a hydrogen atom, and the number of carbon atoms in the alkyl groups is 1 to 3.

$M$  represents Cu (divalent), Zn (divalent), Fe (divalent or trivalent), Sc (trivalent) or lanthanoid elements ( $^{57}La$  to  $^{71}Lu$ ) (trivalent) but preferably represents Sc.

$n$  represents an integer corresponding to the valence of  $M$  and represents 2 or 3.

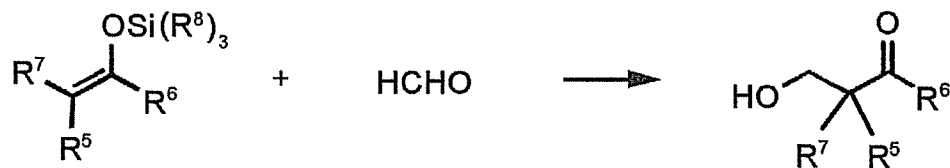
$Y$  represents a halogen atom,  $OAc$ ,  $OCOCF_3$ ,  $ClO_4$ ,  $SbF_6$ ,  $PF_6$  or  $OSO_2CF_3(OTf)$ , preferably  $OTf$ .

[0010]

When this ligand and a Lewis acid represented by  $MY_n$  are mixed in a solvent, a catalyst is formed by coordinating  $M^{n+}$  in the ligand.  $H_2O$ -DME,  $H_2O$ - $CH_3CN$ ,  $H_2O$ -THF,  $H_2O$ -1,4-dioxane,  $H_2O$ -EtOH,  $H_2O$ -MeOH,  $H_2O$ -PrOH, water and the like may be cited as the solvent used. Each concentrations in the solvent is preferably from about 0.01 mole/liter to about 0.1 mole/liter.

[0011]

In the present invention, this catalyst is used in asymmetric hydroxymethylation reactions of formaldehyde and a silicon enolate as described below (chemical formula 3):



$R^5$  to  $R^7$  represent hydrogen atoms, aliphatic hydrocarbon groups, monocyclic or polycyclic alicyclic hydrocarbon groups, monocyclic or polycyclic or aliphatic aromatic hydrocarbon groups or heterocyclic groups and they may also contain substituents. As this hydrocarbon group or the heterocyclic group, alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl and the like, cyclohexyl groups, phenyl groups, phenyl ethyl groups, phenyl vinyl groups, naphthyl groups, furyl groups, thiophene groups and the like may be listed as examples. In addition, a variety of substituents such as halogen atoms, alkoxy groups, thio ether groups, hydrocarbon groups and the like may be listed as substituents that may be attached to these.

$R^5$  to  $R^7$  are preferably as described below:

$R^5$  represents a hydrogen atom or an alkyl group, and  $R^6$  represents an alkyl group, an alkyl aryl group, an aryl group or a sulfide group. However,  $R^5$  and  $R^6$  may together form a 5 or 6 membered ring, part of which may form an aromatic ring, and the ring comprises carbon atoms and optionally hetero atoms.  $R^7$  represents a hydrogen atom, an alkyl group, an alkyl aryl group or an aryl group.

[0012]

R<sup>8</sup> represents a hydrocarbon group. They may each be identical or different, but the preference is for them to be identical. R<sup>8</sup> is preferably an alkyl group, more preferably an alkyl group containing one to three carbon atoms and most preferably a methyl group.  
[0013]

This reaction is conducted in an aqueous solution or a mixed solvent of water and an organic solvent. At this point, dimethoxy ethane (DME), tetrahydrofuran (THF), acetonitrile, dioxane, alcohols containing no more than four carbon atoms and the like may be cited as the organic solvent that readily blends with water used in the mixed solvent with water. DME, THF, acetonitrile and dioxane are preferred examples. The mix ratio of an organic solvent and water is not particularly restricted, but the mixture generally contains at least 1% by weight of water and the presence of at least 5% by weight is more preferred.

[0014]

The amount of the aqueous solution or mixed solvent used should be appropriately considered. Ordinarily, however, the use of the amount necessary to dissolve the starting material substances and the catalyst, for example, from two times the weight to fifty times the weight is considered.

[0015]

The HCHO/silicon enolate molar ratio in a reaction solution is from 0.1 to 10, more preferably about 0.5 to 2. In addition, the catalyst is used at from 1% by mole to 50% by mole, more preferably from 5% by mole to 20% by mole in the reaction system.

The reaction temperature is ordinarily from -15°C to ambient temperature, more preferably from -15°C to 0°C.

The reaction time may be selected appropriately and from 0.5 hours to 50 hours, for example, is selected.

[0016]

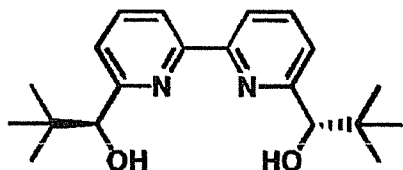
An asymmetric hydroxymethylated compound is formed by this reaction in excellent yield and selectivity, wherein ee is up to around 94%.

[0017]

The present invention is illustrated below by using the examples, but these are not intended to restrict the scope of the present invention.

#### Example 1

A ligand having the structure shown by the formula below was prepared according to the method described in Reference 3. The synthesis route is shown in Figure 1.



DME (0.50 ml) was added to Sc(OTf)<sub>3</sub> (0.9 mg, 0.020 mmole) that had been dried for an hour at 200°C under vacuum. The ligand (7.9 mg, 0.024 mmole) synthesized above was added to this solution, and the mixture was agitated at room temperature until it became

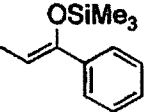
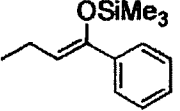
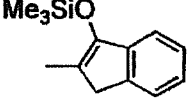
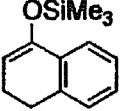
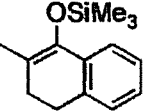
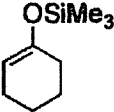
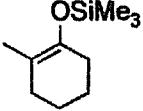
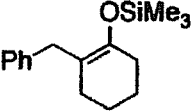
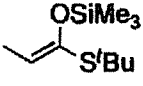
clear. The solution was cooled to  $-20^{\circ}\text{C}$ , and an aqueous HCHO solution (85.8 mg, 35% w/w, 1.0 mmole) and the silicon enolate (41.3 mg, 0.200 mmole) derived from propiophenone, the structure of which is shown in Table 1, were subsequently added. The mixture was agitated for twenty-four hours, and a saturated aqueous sodium bicarbonate solution was subsequently added. The aqueous layer was extracted three times using  $\text{CH}_2\text{Cl}_2$ . The organic layer was dried using  $\text{Na}_2\text{SO}_4$ , the solvent was removed by distillation under reduced pressure, and the residue was purified using silica gel thin layer chromatography (hexane:AcOEt = 2:1).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.24 (d, 3H,  $J = 7.1$  Hz), 2.35 (brs), 3.68 (ddq, 1H,  $J = 4.3, 7.0, 7.1$ ), 3.80 (dd, 1H,  $J = 4.3, 11.1$  Hz), 3.94 (dd, 1H,  $J = 7.0, 11.1$  Hz), 7.48 (dd, 2H,  $J = 7.3, 8.5$ ), 7.58 (t, 1H,  $J = 7.3$ ), 7.97 (d, 2H,  $J = 8.5$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.5, 42.9, 64.5, 128.4, 128.7, 133.3, 136.1, 204.4; IR (neat) 3415, 2936, 1681, 1448, 974, 704  $\text{cm}^{-1}$ ; MS  $m/z$  164 ( $\text{M}^+$ ); Anal. Calcd for  $\text{C}_{10}\text{H}_{12}\text{O}_2$ : C, 73.15; H, 7.37. Found: C, 72.87; H, 7.40; HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 19/1, flow rate = 1.0 mL/min) R isomer:  $t_R = 20.0$  min, S isomer:  $t_R = 17.2$  min.

#### Examples 2-9

The silicon enolates shown in Table 1 were allowed to undergo the same reaction described in Example 1 using the reaction time described in the same table. The yield and optical purity of the asymmetric hydroxymethylated compounds formed in Examples 1-9 are shown in Table 1. The data indicate that asymmetric hydroxymethylated compounds were formed in high yields.

[Table 1]

Example	Silicone Enolates	Time (h)	Yield (%)	ee(%)
1		24	80	90
2		30	66	88
3		14	90	90
4		28	8	66
5		20	80	94
6		29	22	62 <sup>a)</sup>
7		20	68	91 <sup>a)</sup>
8		19	77	67
9 <sup>b)</sup>		24	31	93

a) ee was determined by HPLC analysis of its benzoate

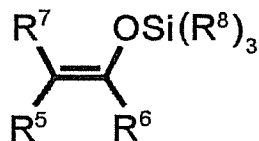
b) HCHO (10 equiv), H<sub>2</sub>O/DME = 1/4Potential Industrial Applicability

[0019]

The asymmetric hydroxymethylated compounds formed according to the method of the present invention are useful as synthetic intermediates and the like for various chemical products.

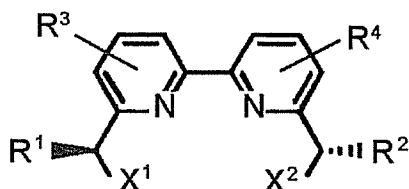
What is claimed is:

1. A method for producing an asymmetric hydroxymethylated compound, comprising reacting a silicon enolate and formaldehyde, in the presence of a catalyst, in an aqueous solution or a mixed solvent of water and an organic solvent, wherein the silicon enolate is represented by the following formula (chemical formula 2):



wherein R<sup>5</sup> to R<sup>7</sup> are hydrogen atoms, aliphatic hydrocarbon groups, monocyclic or polycyclic alicyclic hydrocarbon groups, monocyclic or polycyclic aromatic or aliphatic hydrocarbon groups or heterocyclic groups and R<sup>8</sup>, may be identical or different, are hydrocarbon groups, and

the catalyst is obtained by mixing a ligand or its symmetric isomer and a Lewis acid, wherein the ligand is represented by the following formula (chemical formula 1):

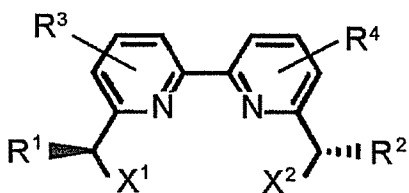


wherein R<sup>1</sup> and R<sup>2</sup>, may be identical or different, are hydrogen atoms, alkyl groups or aryl groups, at least one of R<sup>1</sup> and R<sup>2</sup> contains at least three carbon atoms, R<sup>3</sup> and R<sup>4</sup>, may be identical or different, are hydrogen atoms, alkyl groups containing one to four carbon atoms or alkoxy groups, X<sup>1</sup> and X<sup>2</sup>, may be identical or different, are represented by -OH, -SH or -NHR<sup>9</sup>, wherein R<sup>9</sup> is a hydrogen atom or an alkyl group, and the Lewis acid is represented by MY<sub>n</sub>, wherein M is Cu, Zn, Fe, Sc or a lanthanoid element, Y is a halogen atom, OAc, OCOF<sub>3</sub>, ClO<sub>4</sub>, SbF<sub>6</sub>, PF<sub>6</sub> or OSO<sub>2</sub>CF<sub>3</sub> and n is 2 or 3.

2. The method as of claim 1, wherein R<sup>5</sup> is a hydrogen atom or an alkyl group, R<sup>6</sup> is an alkyl group, an alkyl aryl group, an aryl group or a sulfide group in which R<sup>5</sup> and R<sup>6</sup> may together form a five to six membered ring comprising carbon atoms and optional hetero atoms wherein sections of the ring may form an aromatic ring, R<sup>7</sup> is a hydrogen atom, an alkyl group, an alkyl aryl group or an aryl group and R<sup>8</sup>, may be identical or different, are alkyl groups.

A catalyst is obtained by mixing a ligand or its symmetric isomer and a Lewis acid, wherein the ligand is represented by the following formula (chemical formula 1):



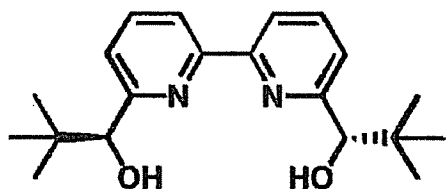


wherein  $R^1$  and  $R^2$ , may be identical or different, are hydrogen atoms, alkyl groups or aryl groups, at least one of  $R^1$  and  $R^2$  contains at least three carbon atoms,  $R^3$  and  $R^4$ , may be identical or different, are hydrogen atoms, alkyl groups containing one to four carbon atoms or alkoxy groups,  $X^1$  and  $X^2$ , may be identical or different, are represented by  $-OH$ ,  $-SH$  or  $-NHR^9$ , wherein  $R^9$  is a hydrogen atom or an alkyl group, and the Lewis acid is represented by  $MY_n$ , wherein  $M$  is Cu, Zn, Fe, Sc or a lanthanoid element,  $Y$  is a halogen atom, OAc,  $OCOCF_3$ ,  $ClO_4$ ,  $SbF_6$ ,  $PF_6$  or  $OSO_2CF_3$  and  $n$  is 2 or 3.

#### Abstract

The present invention presents a catalyst that allows asymmetric hydroxymethylation reactions to progress with excellent asymmetric selectivity and a production method for asymmetric hydroxymethylated compounds using the catalyst.

Asymmetric hydroxymethylated compounds are obtained with excellent asymmetric selectivity by using a catalyst obtained by mixing chiral ligands (for example, chemical formula 4)



with scandium triflate and the like.